Supporting Information

Rapid and efficient solvent-free synthesis of cyclophanes based on bipyridinium under mechanical ball milling

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Experimental sections

^{1}H and ^{13}C NMR spectra were recorded on Brucker AM 300 and 400 spectrometer with tetramethylsilane as the internal standard. Mass spectra were measured on a MALDI-TOF-MS instrument. The solvent-free synthesis was reacted on Retsch MM400 mixer mill. The solid state molecular structure was characterized by X-ray crystallography. Melting points were uncorrected.

The starting materials were commercially available unless otherwise stated. All the solvents used were of analytical grade and dried [MeCN (from P_2Q_5)] if necessary according to standard procedures before use. Thin-layer chromatography (TLC) was carried out on sheets coated with silica gel 60. Column chromatography was performed on silica 60 (300-400 mesh).

1,4-bis(bromomethyl)-2-nitrobenzene(2a)

N-Bromosuccinimide (22.25 g, 0.125 mol) and AIBN (5 mg) were added to a solution of 1,4-dimethyl-2-nitrobenzene **1a** (7.56 g, 0.05 mol) in CCl_4 (120 mL). The suspension was refluxed for 24 h, and later succinimide was observed to float on the surface of the CCl_4 when the solution was cooled down to room temperature. The succinimide was filtered and washed with CCl_4 (50 mL) and then dried under vacuum. The solution was cooled in the refrigerator for two days, thereafter a yellow solid was separated out as precipitate. The solid was filtered and recrystallized from petroleum ether to afford compound **2a** as a white solid (2.03 g, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.07 (d, J = 1.8Hz, 1H), 7.64 (dd, J_1 = 1.8 Hz, J_2 = 1.9 Hz, 1H), 7.56 (d, J = 6.9 Hz, 1H), 4.82 (s, 2H), 4.50 (s, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 139.94, 134.00, 133.13, 132.78, 125.87, 30.44, 28.32.

3,5-bis(bromomethyl)phenol (2b)

$LiAlH_4$ (0.28 g, 7.50 mmol) was added to dry diethyl ether (15 mL) and stirred at 0 ^{o}C for 30 min. Then, a solution of $AlCl_3$ (1.00 g, 7.50 mmol) in diethyl ether (15 mL) was added dropwise as well as the solution of **1b** (1.01 g, 3.00 mmol) in dry diethyl ether (15 mL) after stirring at room temperature for 30 min. 60 min later, the excess $LiAlH_4$ was destroyed by the addition of 15 mL of ethyl acetate, followed by the dropwise addition of 15 mL H_2O. Stirring was continued until all the solids had dissolved, and then the layers were seperated. The aqueous layer was extracted three times with diethyl ether, and the combined organic layers were washed with brine and dried with $MgSO_4$. Filtration and evaporation of the solvent afforded a white solid (0.75 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (s, 3H), 4.7 (s, 2H), 4.48 (s, 2H), 1.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 142.29, 138.72, 128.76, 127.42, 64.54, 32.70.

1,1'-[(2-nitro-1,4-phenylene)bis(methylene)] bis-4,4'-pyridylpyridinium bis (hexafluorophosphate) (3a)

A solution of **2a** (1.32 g, 5 mmol) in dry MeCN (90 mL) as added over 3 h to a solution of 4,4'-bipyridine (2.34 g, 15 mmol) in dry MeCN (5 mL), which was heated under reflux for 18 h. After the solution was cooled to room temperature, the yellow precipitate was filtered and washed with MeCN (20 mL) and Et_2O (20 mL), before being dissolved in H_2O (5 mL). The solid was then dissolved in hot water, and a saturated aqueous solution of NH_4PF_6 was added to it until no further precipitation was observed. The precipitate was filtered and was with H_2O (5 mL), MeOH (5 mL), and Et_2O (5 mL). Finally, we could obtain compound **3a** as a white solid (2.78 g, 74%). m.p.: 240.9-242.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.39 (d, J = 6.8 Hz, 2H), 9.19 (d, J = 6.8 Hz, 2H), 8.91 (d, J = 6.2 Hz, 2H), 8.88 (d, J = 6.1 Hz, 2H), 8.72 (d, J = 6.9 Hz, 2H), 8.67 (d, J = 6.9 Hz, 2H), 8.63 (d, J = 1.3Hz, 1H), 7.98-8.06 (m, 5H), 7.29 (d, J = 8.1 Hz, 2H), 6.27 (s, 2H), 6.01 (s, 2H). ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 153.78, 153.53, 151.48, 148.20, 146.58, 145.97, 141.21, 136.76, 135.61, 131.38, 130.93, 126.92, 126.24, 122.40, 61.75, 60.50.

1-[3,5-bis(hydroxymethyl)benzyl]-4-(pyridin-4yl)pyridinium hexafluorophosphate (3b)

4,4'-bipyridine (1.69 g, 10.8 mmol) was dissolved in 10 mL CH_3CN, heated to 80 °C. To this stirred solution 3,5-bis(hydroxymethyl)benzylbromide (0.5 g, 2.1 mmol) dissolved in CH_3CN (80 mL) was added slowly over 8 h. The solution was cooled to RT and the solvent was removed under reduced pressure. The residue was partitioned between water (100 mL) and dichloromethane (100 mL), washed with dichloromethane to remove excess 4,4'-bipyridine. The aqueous solution was then concentrated to 50 mL, heated to 50 °C, 3 mL of 3 M NH_4PF_6 solution was added. The solution turned hazy and yield **3a** as pale blue solid (0.64 g, 65%). m.p.: 196.2-198.6 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.28 (d, J = 6.3 Hz, 4H), 8.88 (d, J = 5.1 Hz, 4H), 8.64 (d, J = 6.3 Hz, 4H), 8.02 (d, J = 5.3 Hz, 4H), 7.60 (s, 1H), 7.55 (s, 2H), 5.90 (s, 4H), 5.46 (t, J = 5.2 Hz, 1H), 4.53 (d, J = 5.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 153.42, 151.46, 145.86, 145.36, 141.23, 135.35, 127.98, 127.86, 126.25, 122.41, 63.11, 62.54.

8-nitro-5,12,19,26-tetraazoniaheptacyclo[24.2.2.$2^{2,5}$.$2^{7,10}$.$2^{12,15}$.$2^{16,19}$.$2^{21,24}$]-tetraconta-2,4,7,9,12,14,16,18,21,23,26,28,29,31,33,35,37,39-octadecaenetetrakis(hexafluorophosphate) (4a)

1.Method A

1,4-bis(bromomethyl)benzene **2a** (0.1081 g，0.35 mmol), template **6** (0.3532 g，1.05 mmol), and bipyridinium salt **3a** (0.3005 g,0.35 mmol) were dissolved in anhydrous MeCN (300 mL), NaI (5 mg) was added to the clear solution under the protection of N_2 gas. The solution was maintained at -10 °C for 14 days. Then, the reaction mixture was stirred at room temperature (20 °C) for 20 days; the purple precipitate was filtered and washed with MeCN (10 mL) and then dried under vacuum to provide a purple solid, which was dissolved in hot water (10 mL). The aqueous solution was extracted continuously with CH_2Cl_2 for 2 days. During this time, the aqueous solution changed from deep purple to very pale yellow. The aqueous solution was concentrated and the residue was dissolved in hot water (5 mL). This aqueous solution was passed through a short column of silica gel with MeOH/aqueous NH_4Cl solution (2M) (7:3). The nitro-containing fractions were combined and evaporated in vacuo without heating. The residue was dissolved in H_2O, and the saturated aqueous NH_4PF_6 was added to it until no further precipitate was washed with H_2O (5 mL), MeOH (5 mL), and Et_2O (5 mL). After drying under vacuum, the novel cyclophane was recovered as a white solid (0.0935 g, 24%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.46 (s, 4H), 9.38 (d, J = 6.2 Hz, 2H), 9.27 (d, J = 6.2 Hz, 2H), 8.71 (d, J = 6.2 Hz, 2H), 8.67 (d, J = 6.2 Hz, 2H), 8.63 (d, J = 6.1 Hz, 4H), 8.51 (s, 1H), 7.71 (s, 4H), 7.32 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 6.20 (s, 2H), 6.01 (s, 2H), 5.84 (s, 4H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 149.33, 148.77, 148.67, 148.27, 147.79, 146.34, 145.86, 145.24, 138.00, 136.44, 136.33, 133.84, 132.55, 130.24, 130.18, 127.48, 127.21, 127.17, 126.92, 126.06, 63.61, 62.28, 59.97. MALDI-TOF-MS (m/z): Calcd for $C_{36}H_{31}F_{24}N_5O_2P_4$: 1000.1403 ($[M\text{-}PF_6]^+$). Found: 1000.1420 ($[M\text{-}PF_6]^+$).

2. Method B

A mixture of template **6** (0.2016 g，0.6 mmol), and bipyridinium salt **3a** (0.1502 g, 0.2 mmol) was dissolved in anhydrous MeCN (5 mL)，and put into the refrigerator for an hour. Equal quality silica gel was added into it, and then evaporated in vacuo without heating. The assembled complexes and 1,4-bis-(bromomethyl)benzene (0.0618 g, 0.2 mmol) were together with a stainless ball of 7.0 mm diameter, into a stainless jar (5 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparantus and were vibrated vigorously at a rate of 30 Hz at room temperature for 0.5 h. After that, the reaction mixture was collected and dissolved in water. The aqueous solution was extracted continuously with CH_2Cl_2 for 2 days. This aqueous solution wa s passed through a short column of silica gel with MeOH/aqueous NH_4Cl solution (2M) (7:3). The nitro-containing fractions were combined and evaporated in vacuo without heating. The residue was dissolved in H_2O, and the saturated aqueous NH_4PF_6 was added to it until no further precipitate was washed with H_2O (5 mL), MeOH (5 mL), and Et_2O (5 mL). After drying under vacuum, the novel cyclophane was recovered as a white solid (0.052 g, 23%), which provided identical analytical data to the product isolated using method A.

5,13,20,27-tetraazoniaheptacyclo[25,2,2,2^{2,5},1^{7,11},2^{13,16},2^{17,20},2^{22,25}]tetraconta-9-hydroxymethyl-1(28),2,4,7,9,12,14,16,18,21,23,26,29,31,33,35,37,39-octadecaene (4b)

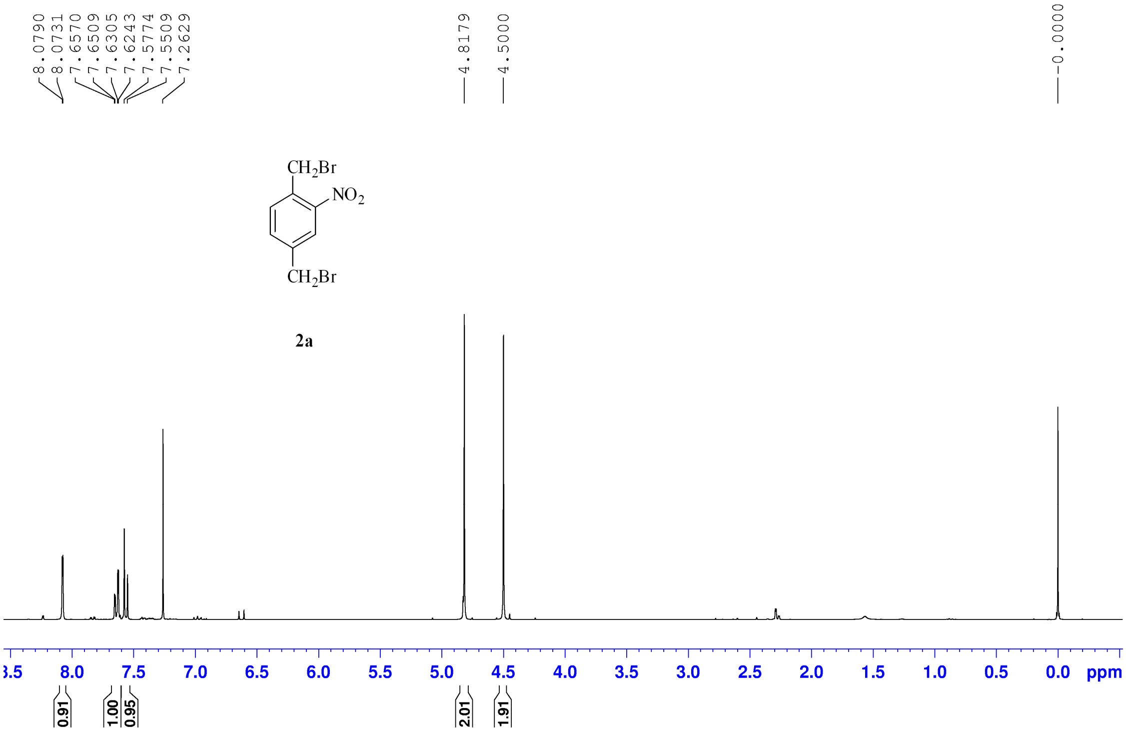
The same procedure as **4a** was applied to obtain **4b**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.47 (d, J =6.8 Hz, 4H), 9.43 (d, J = 6.8 Hz, 4H), 8.46 (d, J = 6.8 Hz, 4H), 8.43 (d, J = 7.9 Hz, 8H), 5.47 (s, 1H), 4.52 (s, 2H). ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 148.90, 148.76, 145.21, 144.88, 144.73, 136.93, 135.59, 129.77, 128.59, 127.17, 126.99, 63.57, 61.97. MALDI-TOF-MS (m/z): Calcd for $C_{37}H_{34}F_{24}N_4OP_4$: 987.1815 ($[M-PF_6]^+$), 842.2173($[M-2PF_6]^{2+}$). Found: 987.1949 ($[M-PF_6]^+$), 842.2264 ($[M-2PF_6]^{2+}$).

5,12,19,26-tetraazoniaheptacyclo[24.2.2.2^{2,5}.2^{7,10}.2^{12,15}.2^{16,19}.2^{21,24}]-tetraconta-2,4,7,9,12,14,16,18,21,23,26,28,29,31,33,35,37,39-octadecaenetetrakis(hexafluorophosphate) (4c)

^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.45 (d, J = 5.0 Hz, 4H), 8.65 (d, J = 5.0 Hz, 4H), 7.72 (s, 4H), 5.01 (s, 4H).

8-fluorine-5, 12, 19, 26-tetraazoniaheptacyclo[24.2.2.2$^{2, 5}$.2$^{7, 10}$.2$^{12, 15}$.2$^{16, 19}$.2$^{21, 24}$]-tetraconta-2, 4, 7, 9, 12, 14, 16, 18, 21, 23, 26, 28, 29, 31, 33, 35, 37, 39-octadecaene tetrakis (hexafluorophosphate) (4d)

^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.46 (t, J = 6.8 Hz, 6H), 9.30 (d, J = 6.4 Hz, 2H), 8.62-8.68 (m, 8H), 7.89 (t, J = 8.3 Hz, 1H), 7.72 (s, 4H), 7.62 (t, J = 6.5 Hz, 2H).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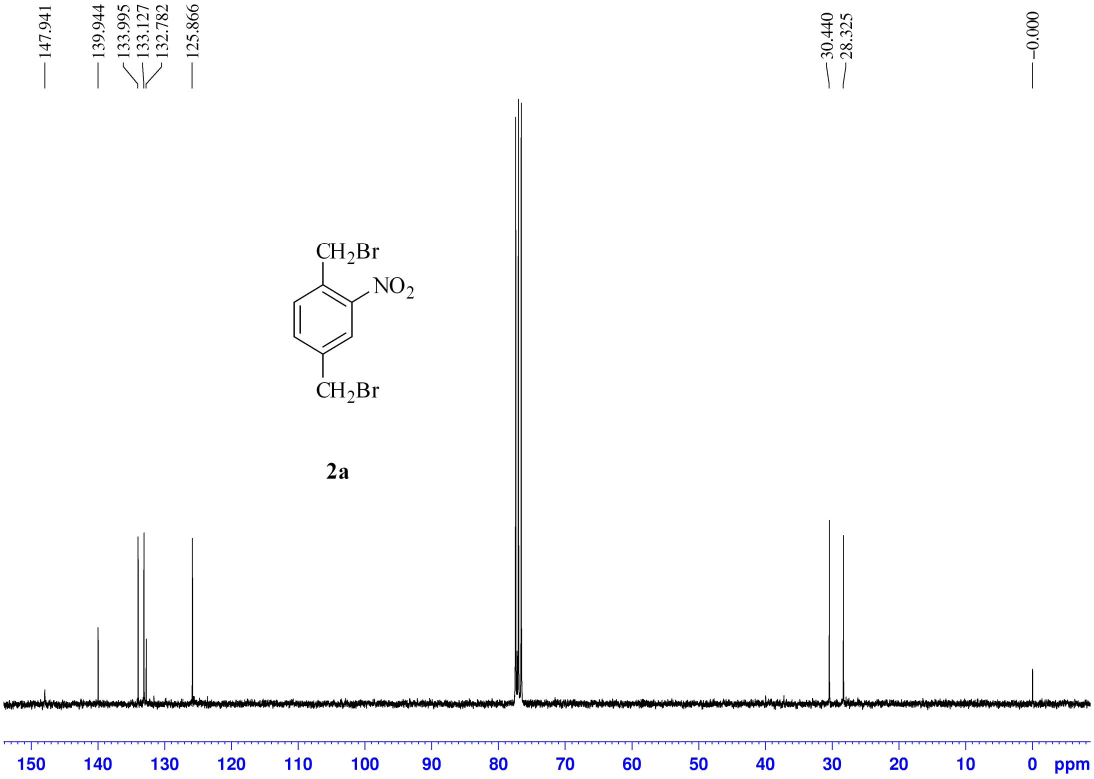
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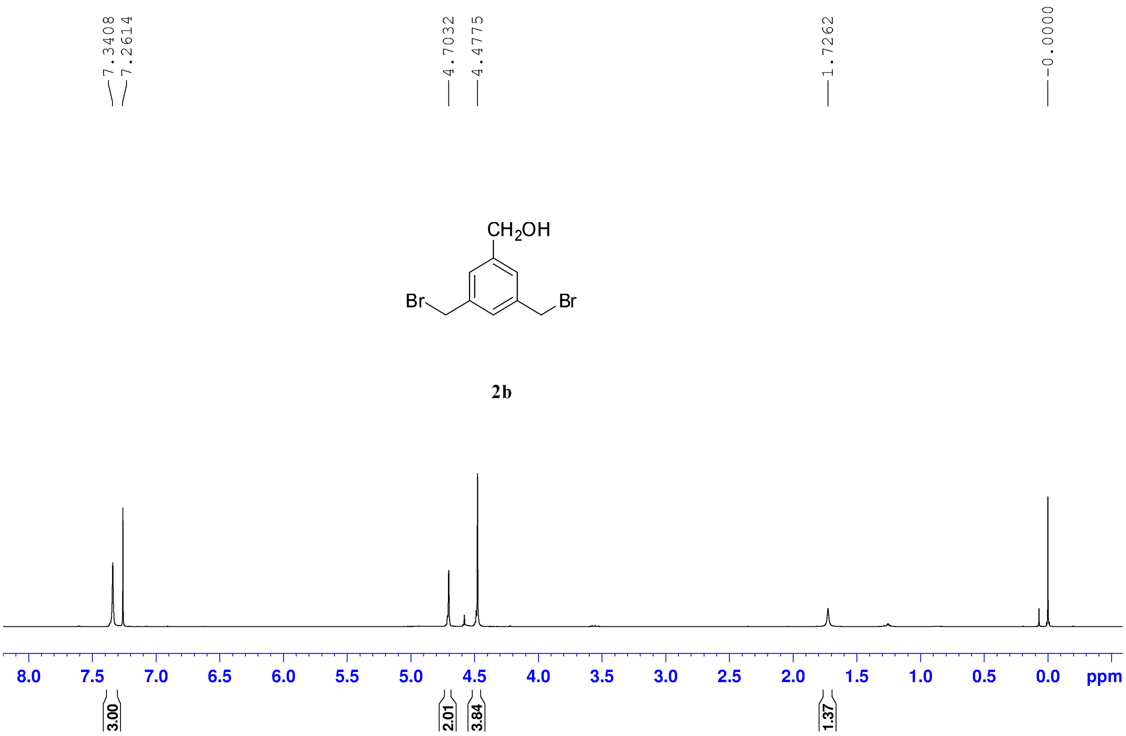
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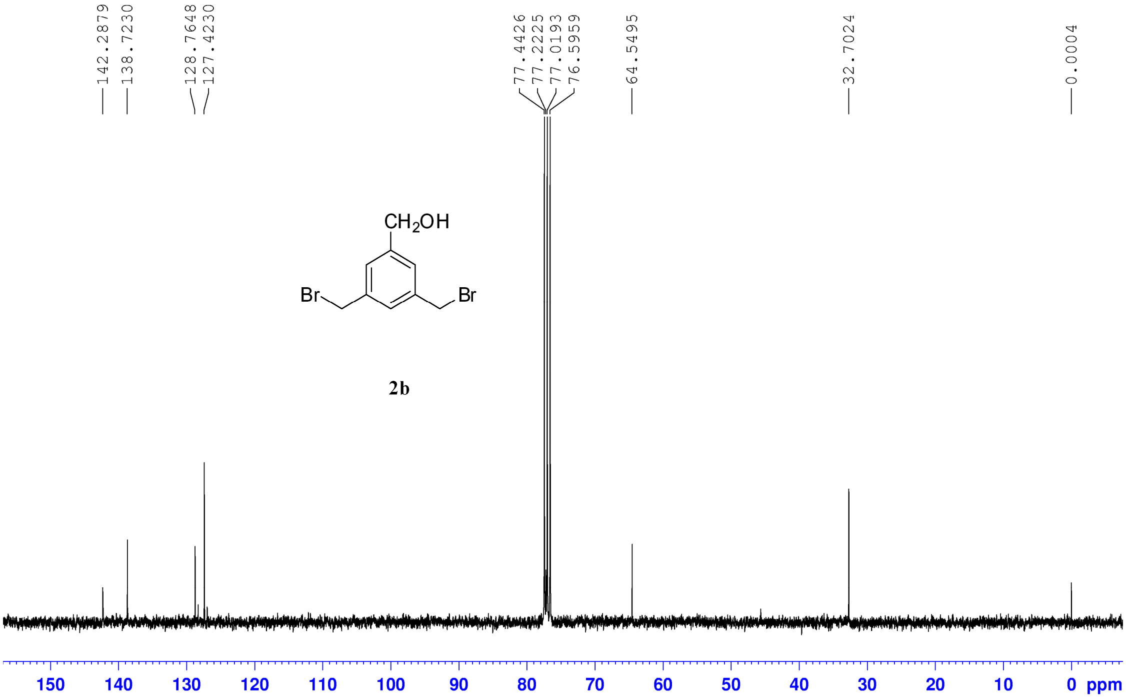
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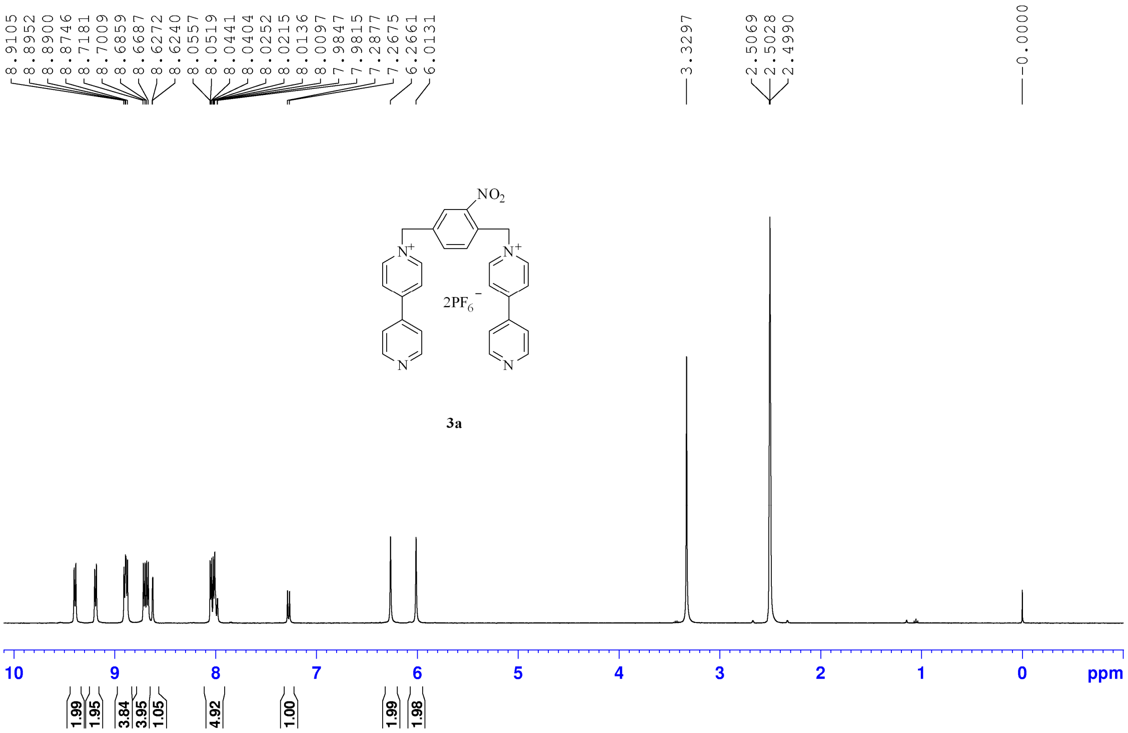
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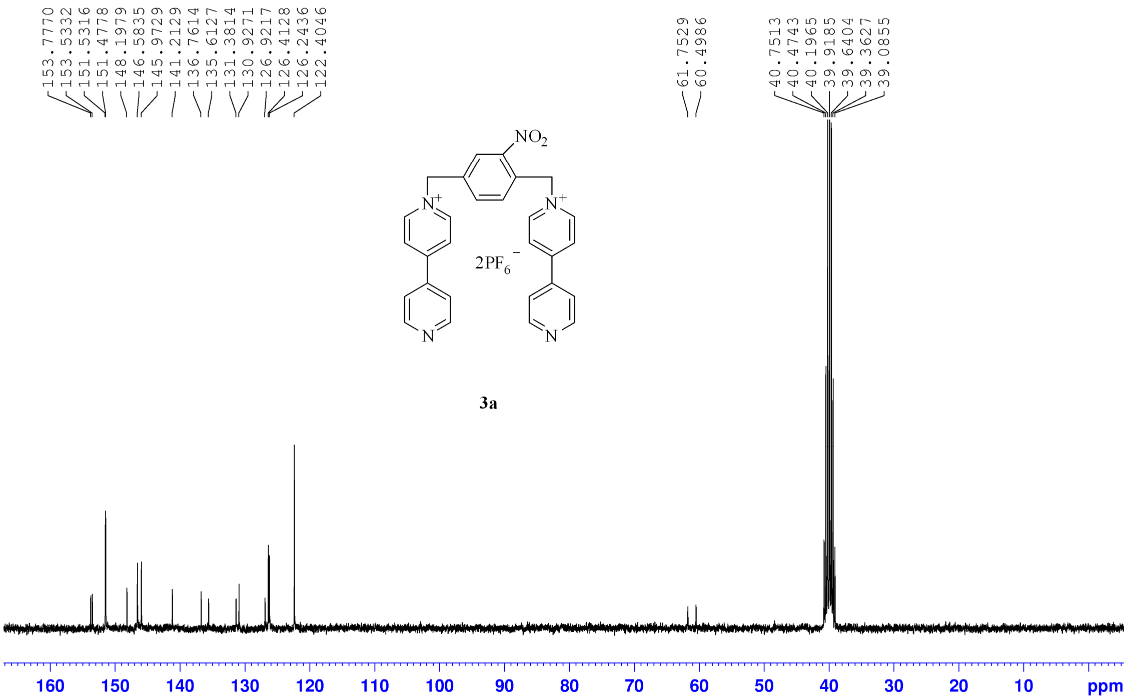
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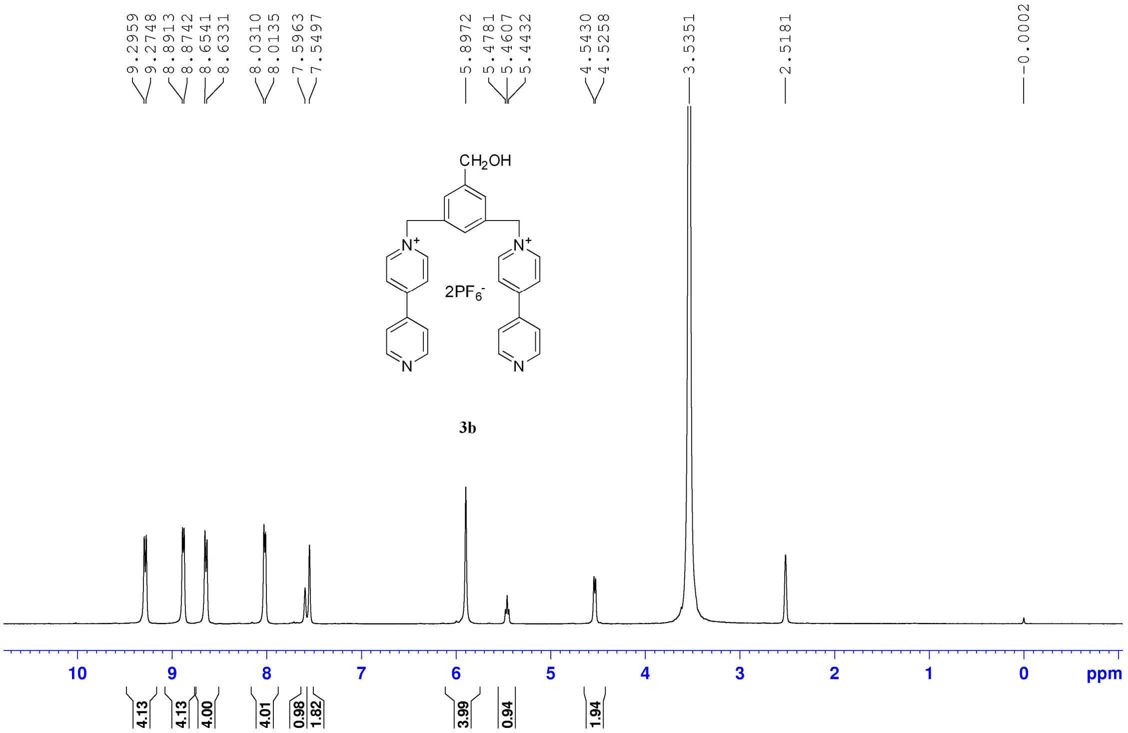
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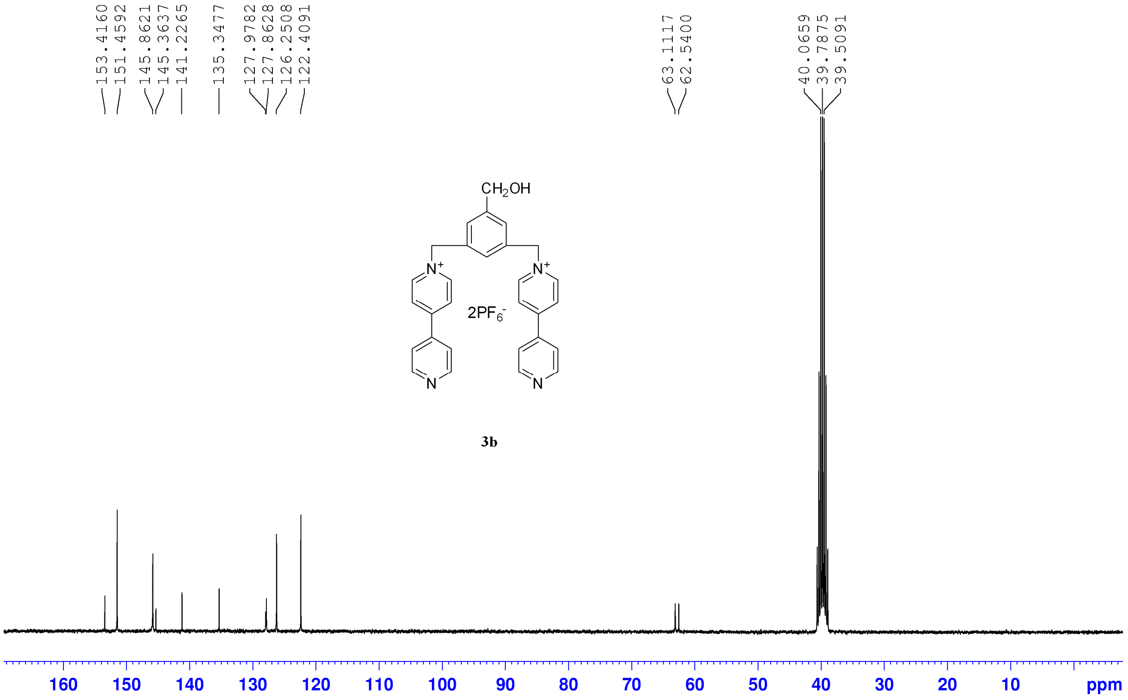
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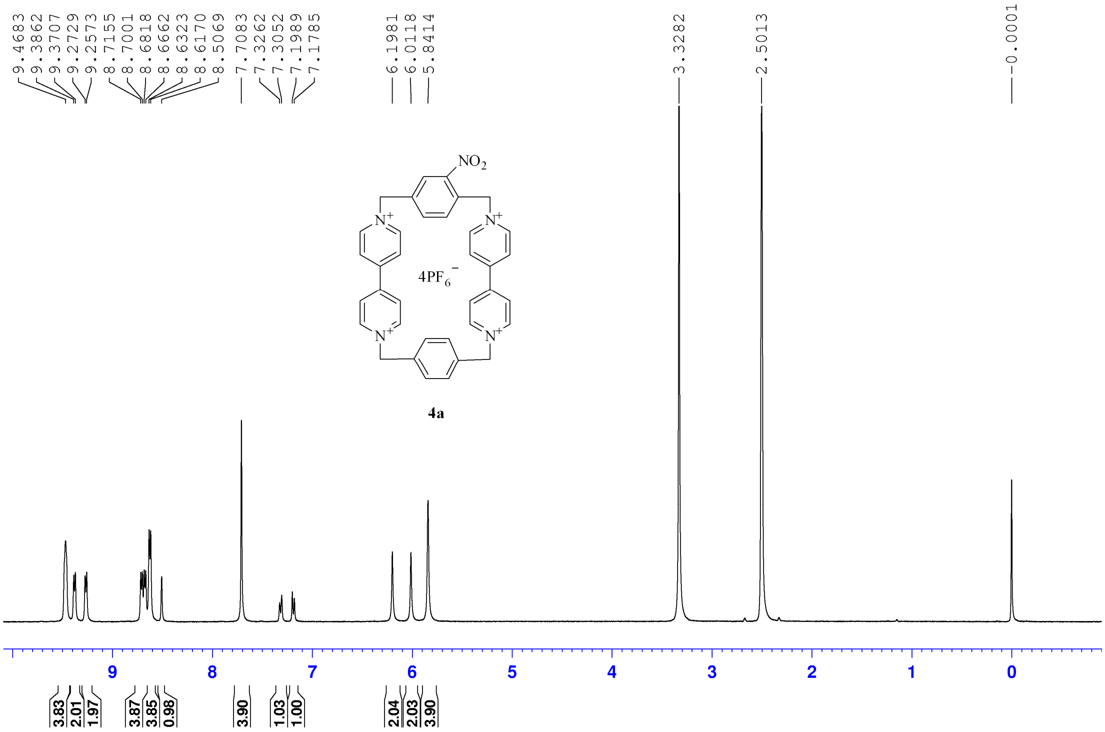
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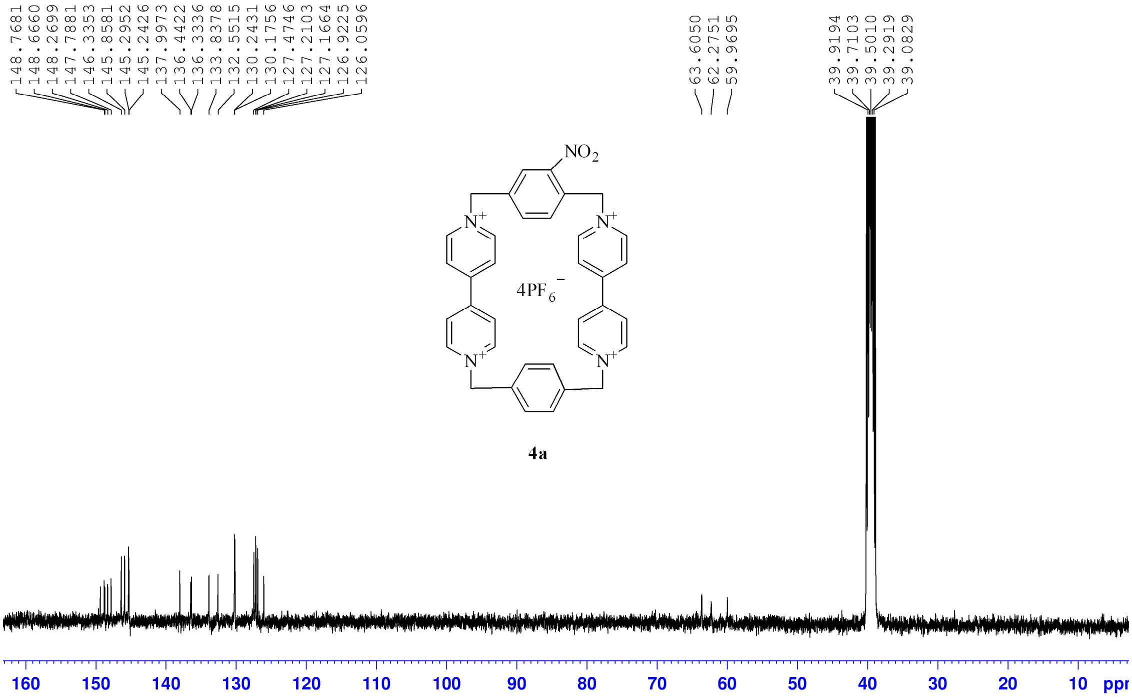
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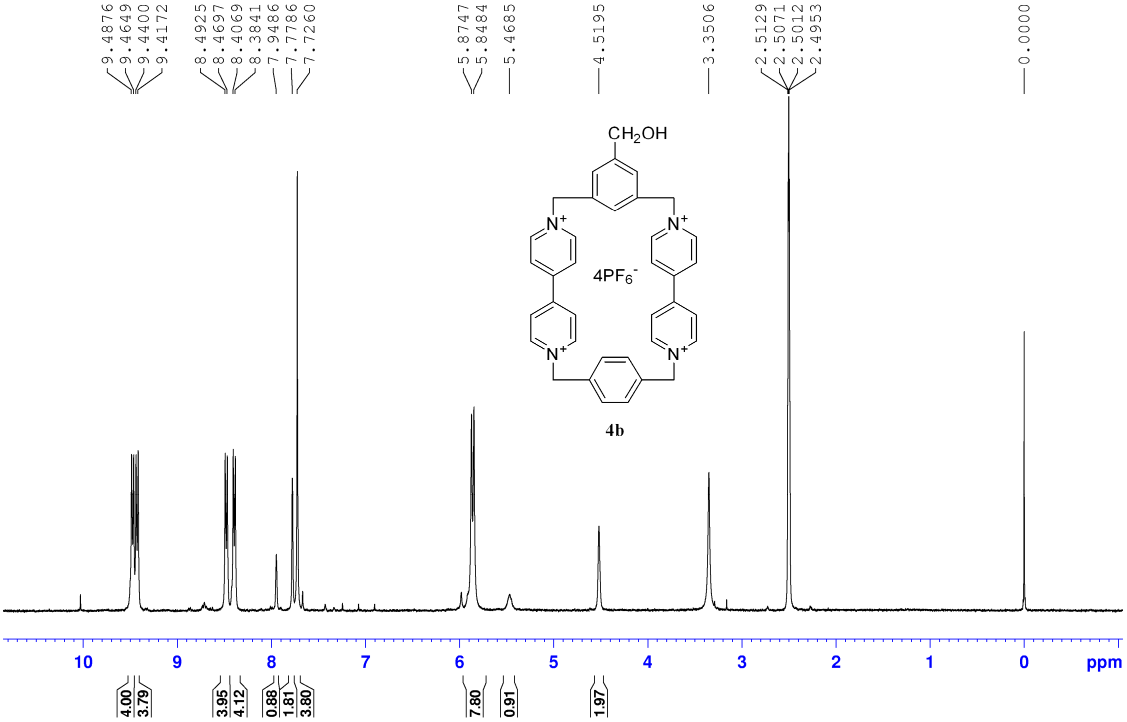
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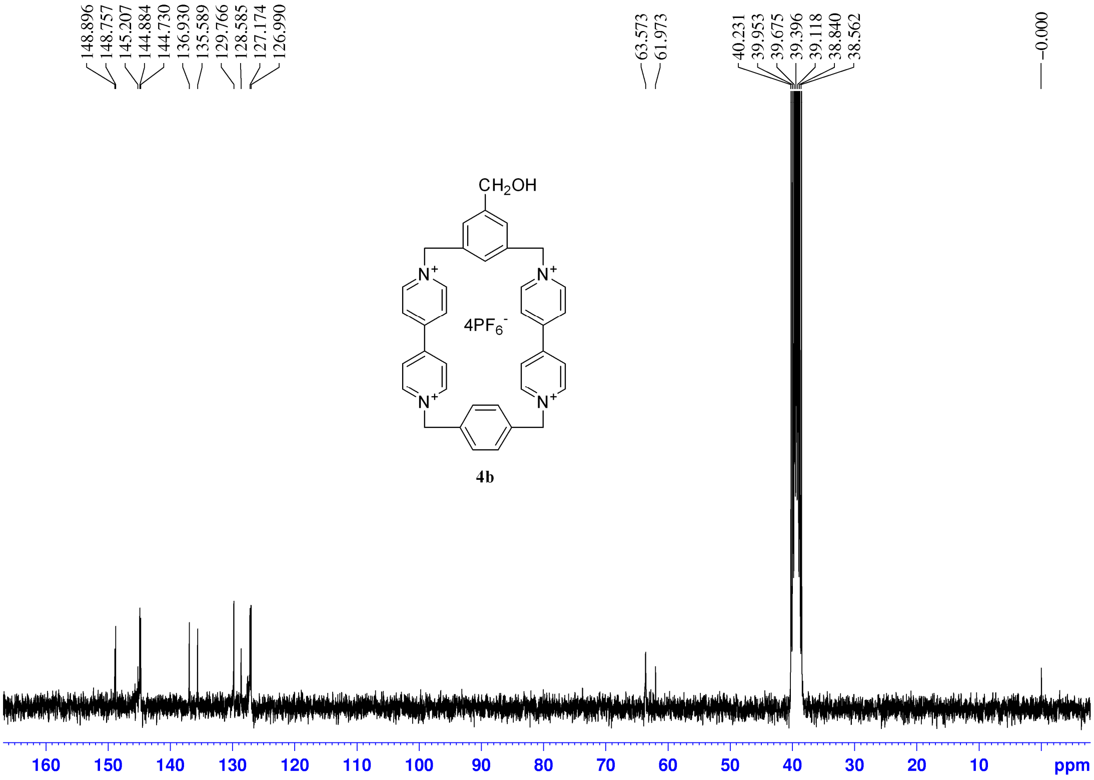
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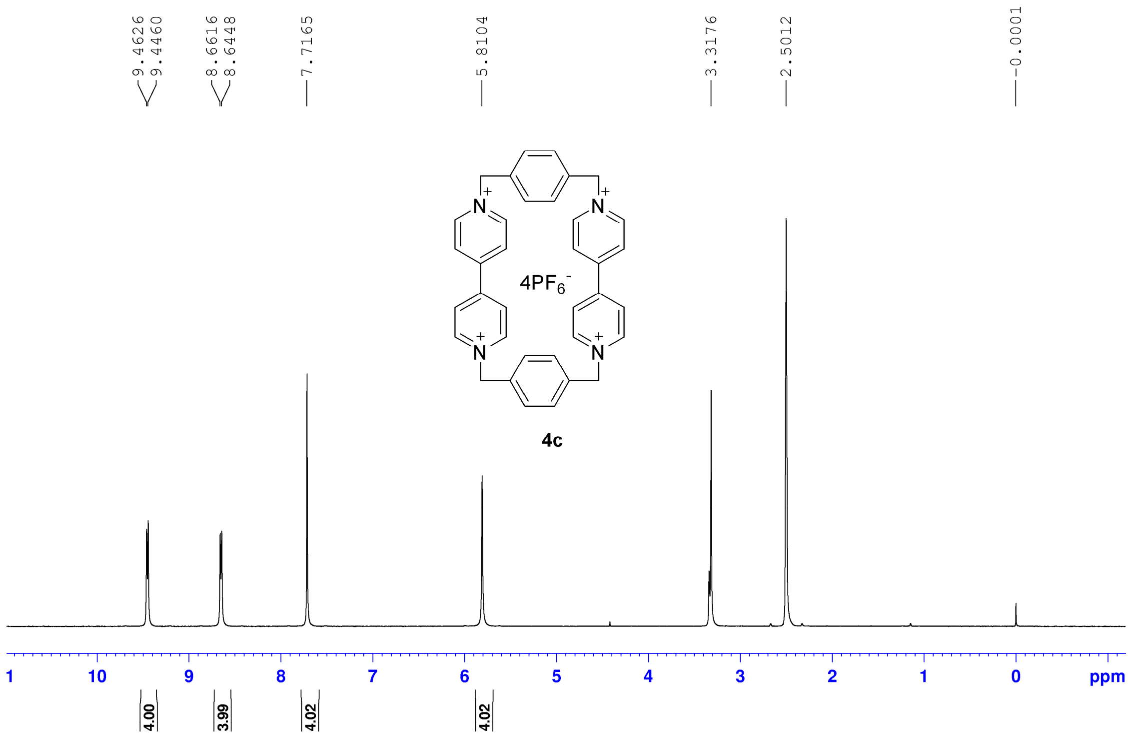
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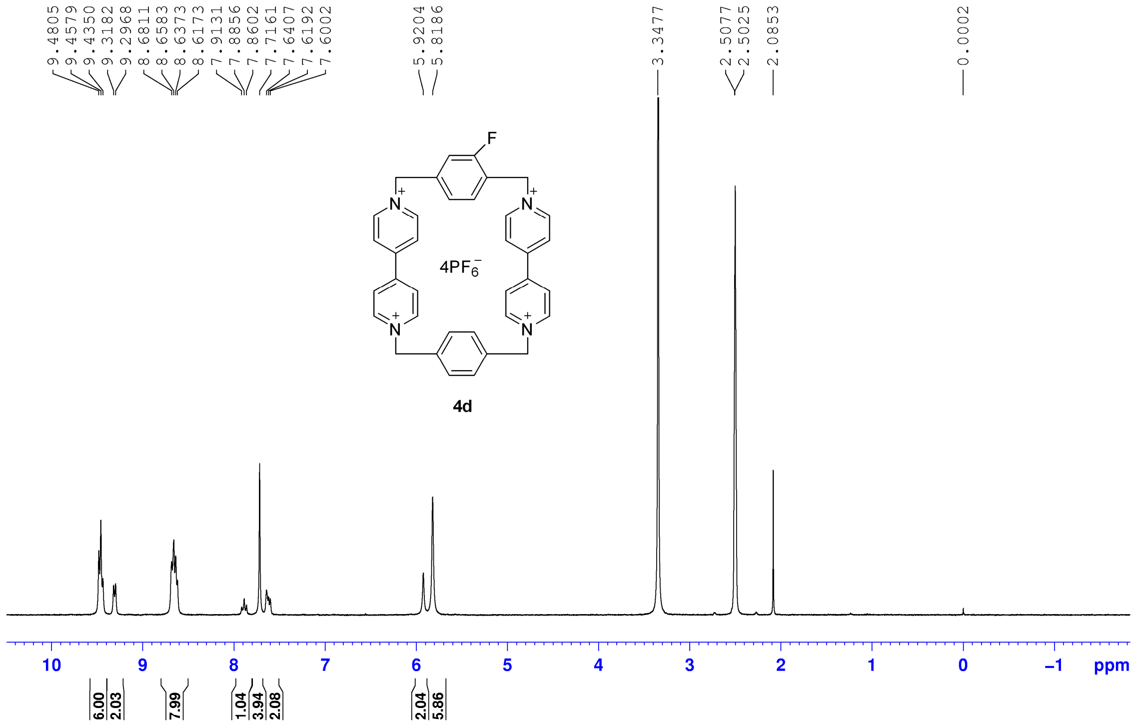
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